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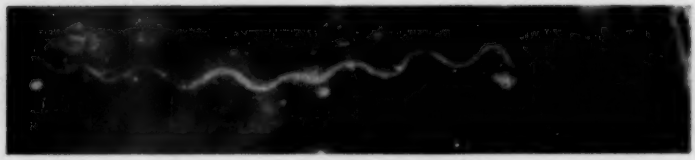

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CONTENTS

Editorial:

Can We Eradicate Venereal Disease? 2

Articles:

Application of the "Semi-Micro" Method to the Evaluation of Antiseptics by E. G. Klarmann, E. S. Wright and V. A. Shternov 5

The Search for Better Antimalarial Drugs by A. S. Alving 15

A Wound Healing Preparation from the Leaves of the Large Plantain (Plantago Major L.) by R. K. Aliev (translated by E. Y. Allen) 24

Selected Abstracts 27

Book Reviews 42

EDITORIAL

CAN WE ERADICATE VENEREAL DISEASE?

VENEREAL disease is rapidly assuming the characteristics of a social rather than a medical problem. We have, today, in the group of antibiotic drugs a specific for each of the diseases classified as venereal: syphilis, gonorrhea, lymphogranuloma venereum, granuloma inguinale and chancroid. Not only are the antibiotics highly efficient but they are almost devoid of toxicity, so there can be no valid objection on the part of the diseased that treatment endangers his or her life.

In those few per cent of cases of syphilis, for example, where the disease is refractory to all treatment, individuals can at least be rendered non-infectious to others and thus the spread of infection checked. It is, therefore, for purely social reasons that these diseases continue to exist in the United States in spite of the efforts of the medical profession, the Public Health Service and other agencies working toward their control.

Before any significant change can take place in the solution of this problem, public opinion must be altered in several respects. This is the crux of the whole situation.

The venereal diseases are placed by most laymen in a special category and not considered as other infectious diseases. One often hears a person almost boast of having just recovered from a streptococcic infection but never of a gonococcic! To have been infected with the one organism places a person in a category deserving special attention and even admiration, but when it involves a related organism, it is socially inadmissible. This is explained by the association of gonorrhea with sexual misconduct, and it may well be, but one can easily contract a streptococcic infection by a similar incident. If all sexual improprieties were followed by gonorrhea, the public attitude toward the disease might be justified, but it is the exception rather than the rule—an exception in many cases dictated by pure chance.

Because the venereal diseases are identified with sex, they are surrounded with that veil of secrecy and dogma which makes sex itself so difficult a thing to discuss in a logical straight-forward manner. In no area of human affairs is there more misinformation dispensed, even by those who are presumed to be authorities on the subject.

A patient with syphilis feels that his physician must not violate his confidence and make his illness known to others. Such an attitude is almost never observed with other contagious diseases where quarantine is the accepted procedure. There is absolutely no justification for the failure to quarantine infectious cases of syphilis and to require by law adequate treatment until the individual is either cured or at least non-infectious. A person contracting almost any disease is ready to volunteer a suggestion as to whom among his contacts it might be traced but not so with venereal disease. It requires careful and expert questioning to obtain from such a patient the name of one for whom he should, with all logic, manifest great resentment. Case finding is a very valuable procedure but the public attitude makes it very difficult and lessens its efficiency.

Some physicians, unfortunately, aid and abet the misguided public viewpoint rather than take an unpopular stand. Such physicians hardly deserve to be considered as members of their honorable profession wherein truth has always been placed above public esteem.

Possibly the greatest deterrent to progress in venereal disease control is the attitude of those misguided moralists who see in the constant threat of venereal disease a useful method to insure chastity and morality in youth. Such an attitude is directly comparable to the early objection made to the use of anesthetics during childbirth, namely, that it was God's will that women should suffer in penance for the original sin. It is very doubtful whether morality can ever be achieved through purely negative measures. In our age of enlightened social concepts, fear is not held in good repute as a useful means of producing good behavior.

It would indeed be a simple matter to eradicate venereal disease if public opinion could be so altered to disassociate these diseases with sexual misconduct and to demand and support laws requiring the adequate treatment of every case until no danger of

the spread of infection existed. That this will take place is unlikely until the public attitude toward sex itself is more sound and logical. Possibly here is the vital point of attack before the complete eradication of venereal disease can be achieved. There are signs of progress in this direction, but the surface is only scratched. As long as the subject of sex is taught on theoretical grounds which are entirely unrelated to actual practice, the public attitude will continue to be confused, illogical and an obstacle to social progress. Venereal disease is itself only a symptom of a much deeper underlying illness of society. The treatment of this disease poses the same problems as those met in darkest Africa where superstition and witchcraft for years thwarted the efforts to introduce scientific methods.

L. F. Tice

APPLICATION OF THE "SEMI-MICRO" METHOD TO THE EVALUATION OF ANTISEPTICS

By E. G. Klarmann, E. S. Wright and V. A. Shternov *

Introductory Remarks

THE "semi-micro" method was developed originally in connection with the testing of quaternary ammonium compounds. Its rationale has been given in considerable detail elsewhere (1). It was intended primarily to control a factor, recognized as characteristic for this class of surface active compounds, viz., the creation in the germicide-bacteria mixture of a condition which prevents the transfer of a representative inoculum into the subculture. This condition has been ascribed hypothetically by the authors to a tendency of the bacterial suspension of massing against the walls of the "medication" tube, rather than remaining in a more or less uniform state of dispersion. The formation of clumps under the influence of quaternary ammonium compounds, as postulated by McCulloch and his associates (2), may also be involved in contributing to this phenomenon.

It was assumed that subculturing the entire "medication" mixture (of diluted germicide plus bacteria) would eliminate the sampling error involved in the transfer of a standard loopful which constitutes a regular step in several customary testing methods. This expedient had to be combined, of course, with a complete elimination of bacteriostasis which could have played a disturbing role under the conditions of this procedure, if it had been left uncontrolled. As described in its most recent form (3), the "semi-micro" method calls for the exposure of 0.05 cc. of a 24-hour broth culture to the action of 0.5 cc. of the diluted germicide (representing one-tenth the proportions specified by the F. D. A. method); after the required period of time, the reaction is stopped by dilution with nutrient broth containing a suitable antidote to neutralize any bacteriostatic action of the germicide used. In the case of the quaternary ammonium compounds, Bacto-Oxgall was found to be the most effective antidote for this purpose.

* Lehn & Fink, Inc., Bloomfield, N. J.

General Comments on Requirements of Tests for Antiseptics

The "semi-micro" method suggests itself, on different grounds, for a study of antiseptic substances, with specific reference to the potentially antagonistic matter with which they are likely to come in contact, under the conditions of practical use. In this connection it cannot be stressed sufficiently that the criterion of the fitness of any particular antiseptic, for any particular use, must be its demonstrated capacity of a permanent prevention of bacterial activity under the conditions of such use. Thus, if a given antiseptic is shown to prevent the growth of bacteria in a nutrient medium, but does not prevent it upon subsequent contact of the bacteria with some physiological material (e. g., blood, serum, etc.) then its fitness for use in connection with wound antisepsis or preoperative use is open to serious question.

It is freely conceded that such considerations do not apply to antiseptics which, by their very purpose, are not required to be effective in the presence of tissue fluids. If, for example, an antiseptic is applied to the skin with the sole intent of suppressing body odor caused by the putrefactive action upon perspiratory secretion of the bacterial skin flora, then obviously, it does not matter whether its antibacterial performance is antagonized by blood or by serum. Similar considerations would apply, e. g., to an oral antiseptic wash designed to counteract the action of acidogenic bacteria on teeth.

Tests in the Presence of Blood

In the present study, we were interested in ascertaining the effect of blood (and incidentally that of serum) upon the action of a number of common antiseptic agents. With reference to the *modus operandi* of the "semi-micro" method, it should be stated that these tests were not carried out *in the presence* of the tissue fluids mentioned, but that the test organisms were given an opportunity to come in contact with them *following exposure* to the action of several antiseptics studied. Thus the antiseptics were not interfered with during the period of their action upon the test-organisms; to this extent, the experimental conditions of the method tended to favor the antiseptics tested, as compared with the conditions of use where the antibacterial action often must operate from the very beginning in the presence of the interfering tissue fluids.

The following Table I illustrates the observations made with a number of commonly used non-metallic germicides and antiseptics. *Micrococcus pyogenes aureus* is the test organism (24-hour F. D. A. broth culture of strain 209); the time of contact between the antiseptic dilution and the bacterial suspension is 10 minutes at 20° C.

These results reveal considerable differences in the behavior of the several types of antiseptics studied. Bacteria exposed to the action of the minimum germicidal concentrations of phenol and of phenolic disinfectants (including p-chlorophenol) appear to have been rendered non-viable regardless of their subsequent contact with defibrinated horse blood (present in the form of 10 percent blood broth). Comparatively little variation is observed in the case of two different inorganic hypochlorite preparations containing, respectively, 0.9 and 5.2 percent of active chlorine. The same is true of the two organic chlorine compounds tested, also of Lugol's Iodine Solution. Of the several dyes examined, Brilliant Green appears to be most thoroughly affected by blood in its antibacterial performance. Considerable variation is evident, however, in the case of the three quaternary ammonium compounds tested; this would indicate the risk involved in a comparative estimation of their bactericidal power in the absence of tissue fluids, in connection with any relevant intended use, e. g., in preoperative skin antisepsis. (The three quaternary ammonium compounds are: (a) alkyldimethylbenzylammonium chloride, (b) *p-tert.* octylphenoxyethoxyethyldimethylbenzylammonium chloride, (c) cetylpyridinium chloride.)

Hexachlorodihydroxydiphenylmethane appears to be greatly affected in its action, probably owing to suppression by blood of its strongly bacteriostatic quality. This fact should be borne in mind in connection with any prophylactic formulations intended to guard against infection in the case of injuries involving a break in the skin; it does not appear to be relevant to those uses in which an overall suppression of the bacterial flora is aimed at on the unbroken skin (as, e. g., in the case of an improved surgical scrub-up technique, or in that of a body soap with a deodorant quality).

Table II deals with three organic mercurials and with mercuric chloride in the concentrations of their *aqueous* solutions stated. The negative results obtained when using either regular F. D. A. broth or serum broth are definitely due to bacteriostasis, as ascertained in the customary fashion. While, therefore, the addition of 10 per cent

TABLE I

MINIMUM GERMICIDAL CONCENTRATIONS BY SEMI-MICRO METHOD

Micrococcus pyogenes aureus, 20° C.

Antiseptic	F. D. A. Broth	F. D. A. Broth + 10% Blood	BOG Broth	F. D. A. Broth + 0.5% $Na_2S_2O_3$
Phenol	1:50	1:50		
Cresylic Disinfectant—50%	T:150	1:125		
Fortified Cresylic Disinfectant (p. c. 5)	1:150	1:150		
Synthetic Phenolic Disinfectant (p. c. 10)	1:225	1:175		
Synthetic Phenolic Disinfectant (p. c. 5)	1:100	1:100		
p-Chlorophenol	1:150	1:150		
Hexachlorodihydroxydiphenyl Methane	1:40,000*	1:400*		
Quaternary Ammonium A	1:22,500*	1:2000*	1:1300	
Quaternary Ammonium B	1:25,000*	1:5000*	1:1800	
Quaternary Ammonium C	1:15,000*	1:3000*	1:500	
Hypochlorite Solution (0.9% av. Cl)	1:70	1:50		1:100
Hypochlorite Solution (5.2% av. Cl)	1:400	1:350		1:500
Chloramine T	1:400	1:250		1:500
Azochloramid	1:550	>1:550		>1:550
Lugol's Iodine Solution	1:300	1:300		
Rivanol	1:1000*	>1:1000		
Acriflavine	1:2000*	1:1000*		
Gentian Violet	1:50,000*	1:20,000*		
Brilliant Green	1:50,000*	1:2000*		

* Bacteriostasis.

of horse serum does not eliminate bacteriostasis, that of 10 per cent defibrinated horse blood appears to suppress it in all four cases, paralleling the corresponding effect of thioglycolate, the antidote *par excellence* for mercurial antiseptics. Thus the requirement of using a suitable suppressor of the high bacteriostatic potency of mercurial antiseptics is by no means academic in character; on the contrary, the sulfhydryl groups of the thioglycolate molecule which are concerned in its reactivity with mercury have their structural counterparts in several biological entities (including tissue proteins, enzymes, etc.). It appears, therefore, that infectious microorganisms, inhibited in regard to certain biological manifestations by mercurial antiseptics, have not been deprived of their viability when brought into contact with blood; in other words, blood reverses the antibacterial action of the mercurials tested.

TABLE II

PERFORMANCE OF MERCURIAL ANTISEPTICS BY SEMI-MICRO METHOD
Micrococcus pyogenes aureus, 20° C.

Antiseptic	F. D. A. Broth	F. D. A. Broth +10% Blood	F. D. A. Broth +10% serum	F. D. A. Thioglycolate Broth
Merbromin 1:50	—*	+	—*	+
Nitromersol 1:2500	—*	+	—*	+
Sodium ethylmercurithiosalicylate 1:1000	—*	+	—*	+
Mercuric Chloride 1:1000	—*	+	—*	+

* Bacteriostasis

In view of the findings reported in Table II, it seemed intriguing to extend the period of observation of the four mercurial antiseptics beyond 10 minutes, in order to determine the length of time permitting the recovery of staphylococci following transfer to blood and thioglycolate media respectively.

The following Table III illustrates the results obtained with exposure periods up to 16 hours. The figures in the columns indicate the numbers of tests in which positive or negative findings were made.

TABLE III

LONG TIME EXPOSURE TESTS BY SEMI-MICRO METHOD

	MINUTES										HOURS													
	10		15		20		30		40		1		2		3		4		5		6		8		16	
Antiseptic	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T	B	T
Merbromin 1:50	4+	1+ 2—	3+ 4—	2+	5+ 4—	2+ 1—	5+ 4—	2+ 4—	3+ 4—	1+ 3—	1+ 5—	2—	2—	1—	2—	1—	1—	1—	1—	1—	1—	1—			1—	1—
Nitromersol 1:2500					1+		2+				1+		2+		3+		1+		1—		1+		2+ 3—	2+ 1—	2+ 1—	2+
Sodium ethylmercurithiosalicylate 1:1000	1+		1+		2+		1+				1+		2+		3+				2+		1+		4+	3+	2+ 1—	2+
Mercuric chloride 1:1000	3+ 1—	1+	4—	2+	1+ 5—	3+	3—	3+	3—	3+	1+	1+	1—	1+	1—	1+	1—	1+	1—	1+	1—	1+			1—	1+

B—Blood medium

T—Thioglycolate medium

The following comments apply to the individual mercurial compounds tested:

Merbromin—Staphylococci are gradually dying during the first hour, so that at the end of this period only a few could be recovered by the action of blood or of thioglycolate; none were recovered at the end of the second hour. Bacteriostasis is not neutralized sufficiently by thioglycolate media containing 0.03 per cent of thioglycolic acid. In a separate series of tests the proportion of thioglycolic acid was increased to .06, .1, .15 and even .2 per cent respectively, but no appreciable reduction of bacteriostasis could be achieved. The increase in the proportion of thioglycolic acid does not prevent the growth of the test-organism, although the greatest proportion of .2 per cent reduces it to some extent.

The addition of 10 per cent horse serum to the thioglycolate media, however, improved the conditions for recovery. In one such test the test organism could be recovered after respectively 20, 30, 40 and 60 minutes of exposure to the action of merbromin.

Nitromersol—This mercurial did not appear to kill the test organism uniformly even after 16 hours, although the possibility for survival was decreased materially in the course of the first 5 hours, since after this time no recovery resulted in several instances.

Sodium ethylmercurithiosalicylate—Here, too, recovery could be achieved even after 16 hours, in almost all cases.

Mercuric chloride—There was no recovery by blood after 20 minutes, but thioglycolate effected recovery in all tests even after 16 hours of exposure. The reason for the failure of blood in this case is to be sought in the destructive action of mercuric chloride upon the blood.

Broadly speaking, this information as it relates to mercurials is not new. With respect to the ability of blood to suspend bacteriostasis, it is in agreement with Banti's recent findings (4). In its general aspects it applies not only to mercurial antiseptics as such, but also to other presumably antiseptic or germicidal mercurials intended to prevent systemic infection, such as disinfectants for surgical instruments, for surgical sutures, etc.

Since mercurial antiseptics are frequently applied in the form of tinctures, it was deemed of interest to determine the antibacterial character of the solvent (usually consisting of alcohol 50 parts,

acetone 10 parts, water q. s. 100 parts) by the same "semi-micro" method. Table IV indicates the results of several individual tests obtained with plain F. D. A. broth and with 10 per cent blood broth respectively:

TABLE IV

ANTIBACTERIAL ACTION OF THE SOLVENT USED IN PREPARING TINCTURES OF ORGANIC MERCURIALS

Micrococcus pyogenes aureus, 20° C.

Experiment	5 minutes		7½ minutes		10 minutes		15 minutes	
	F. D. A. Broth	Blood Broth	F. D. A. Broth	Blood Broth	F. D. A. Broth	Blood Broth	F. D. A. Broth	Blood Broth
I	+	+	+	+	+	—	—	+
II			—	—	—	—	—	—
III			—		—	—		
IV			+	+	—	—	—	—

The solvent used in preparing the mercurial tinctures usually appears to be germicidal under the conditions of the "semi-micro" technique. These findings also supply the reason why the tinctures of all three mercurials tested by us were found to be uniformly germicidal in 10 minutes; thus any credit for this germicidal action of the tinctures appears to be due primarily to the solvent used.

Exploratory Studies

A number of experiments were carried out with the idea of determining whether a reversal of antibacterial action might be involved in some of the results obtained with the non-mercurial materials studied. This approach called for a sufficient extension of the reaction time to permit colony counts; it was achieved by the use of "sub-germicidal" concentrations which were applied according to the method described in detail in the experimental part. As shown in Table V, a reversing action appears to underlie the results produced by blood in the cases of hexachlorodihydroxydiphenylmethane, alkyldimethylbenzylammonium chloride, hypochlorite, merbromin aqueous and rivanol; blood is unable to reverse the effect of "sub-germicidal" concentrations of phenol, parachlorophenol and of the fortified cresylic disinfectant.

TABLE V

REVERSAL BY "SUB-GERMICIDAL" CONCENTRATIONS

Micrococcus pyogenes aureus, 20° C.

Antiseptic	Dilution	Number of Colonies per Plate: Salt Solution	Blood
Phenol	1:90	180	150
Parachlorophenol	1:400	64	60
Fortified Cresylic Disinfectant (p. c. 5)	1:500	2835	2520
Hexachlorodihydroxydiphenylmethane	1:4000	50	TMTC*
Alkyldimethylbenzylammonium chloride	1:50000	181	1386
Hypochlorite solution (0.9% av. Cl)	1:150	252	2142
Merbromin aq.	1:100	2	TMTC
Rivanol	1:5000	55	TMTC

* TMTC = Too many to count. In this case as well as in that of Merbromin aq. it was necessary to introduce an extra washing with 10 cc. of saline (followed by centrifuging) in order to avoid bacteriostasis.

Experimental Procedures

1) *"Semi-Micro" Technique*

Pipet 0.05 cc. of a 24-hour F. D. A. broth culture of *Micrococcus aureus 209* onto the bottom of sterile 25 x 150 mm. test tubes. This step must be done with great care so that the pipet does not touch the walls of the test tube. The tubes are placed in a water bath at 20° C. Then 0.5 cc. of diluted disinfectant, which has also been kept in a water bath at 20° C. is added to each tube and thoroughly mixed with the culture. Ten minutes after adding the disinfectant, 20 cc. of F. D. A. broth or of blood broth is poured into the tube using aseptic precautions. The blood broth is prepared the previous day by adding 2 cc. of fresh defibrinated horse blood to 20 cc. of F. D. A. broth and incubating the tubes for 24 hours. The results are read after incubation for 96 hours at 37°C.

2) *Reversal by "Sub-Germicidal" Concentrations*

Place 0.5 of a 24-hour F. D. A. broth culture of *Micrococcus pyogenes-aureus 209* in a 50 cc. centrifuge tube, kept in a water bath at 20° C. Add 5 cc. of the "sub-germicidal" dilution of the antiseptic to each of two tubes. At the end of 10 minutes, centrifuge for 30 minutes and drain off the supernatant liquid. To one tube add 1.5 cc. of defibrinated horse blood, to the other 1.5 cc. of physiological

saline. Stir (and scrape walls) with a platinum loop, fill to 15 cc. with F. D. A. agar of 45° C., invert four times and plate. Incubate for 48 hours.

Conclusion and Summary

The "semi-micro" method, previously suggested for testing quaternary ammonium disinfectants, is adaptable to the screening of antiseptics intended to guard against infection through breaks in the skin and through other similar circumstances.

Defibrinated horse blood affects, in a characteristic fashion, the function of different antibacterial agents under the conditions of this screening procedure, thereby facilitating a selection of those antiseptics which are likely to be effective where contact with tissue fluids (blood, serum) must be anticipated.

It may be demonstrated, by means of a special procedure, that the antagonistic action of blood depends, in several instances, upon its ability to reverse the antibacterial action of some of the antiseptics tested. Mercurials appear to be particularly susceptible to this reversing action.

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THE SEARCH FOR BETTER ANTIMALARIAL DRUGS*

By Alf S. Alving, M. D.**

MALARIA is probably the most important disease in the world. Accurate statistics are unavailable. It is generally agreed that at least three hundred million people are afflicted with the disease and that over three million persons die from it each year. While the most intense effects of malaria occur within the equatorial and subequatorial regions, it has been reported as far North as the Arctic Circle and at the extreme tip of South America. Until recently malaria was a serious problem in the southern part of the United States and was not uncommon throughout most of the country. Although it held intense public interest as the most important medical military problem in the second World War, few indeed realize that it has been a major problem in each of the wars in which we have participated. In fact as recently as the Spanish-American War, malaria and typhoid killed six times as many men as did bullets.

In 1915 the British and French conducted a campaign in the Balkans which was to have more far reaching consequences than could possibly have been foreseen. The Macedonian campaign was undertaken for political objectives—to relieve the hard pressed ally, Serbia, and to check the influence of Germany in the Balkans. Landings were made in Salonika, Greece, against the warnings of several outstanding malariologists. A military campaign was undertaken in a highly malarious area with practically no antimalarial precautions and without adequate training of medical officers in the effective use of quinine or insecticides. The Germans and Austrians opposing the invading forces were without quinine due to the Allied Blockade. By 1916 all armies were immobilized due to the disastrous effects of malaria, and a virtual stalemate was established on the Balkan front for two years. At first this appeared to be of advantage to the

* Presented at the American Pharmaceutical Manufacturers' Association Scientific Award Ceremony on November 29, 1949, at The Waldorf-Astoria, New York City, New York.

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Germans and almost justified their jibe that Salonika was their greatest concentration camp—"an enemy Army, prisoner of itself". However, by 1918 proper antimalarial measures, including the compulsory taking of daily quinine, gave the Allied forces the advantage in the campaign which eventually resulted in the fall of Bulgaria and the first breach in the Germanic Alliance. The Macedonian campaign, therefore, taught the important lesson that malaria fights on the side that can best control it. The Germans with typical foresight took advantage of their bitter experience and inaugurated an extensive program for the synthesis of antimalarial drugs after the war. In 1927 the chemists in the laboratories of I. G. Farbenindustrie at Elberfeld developed a synthetic chemical now called plasmochin or pamaquin.

A word about the diseases which we ordinarily call "malaria." In man there are really four diseases, but only two of these are of importance. One is produced by *Plasmodium vivax* which causes few deaths but has a great tendency to relapse. Vivax malaria is also called *benign tertian malaria* because paroxysms consisting of severe chills, fever and headaches due to the development of new broods of parasites within the red blood cells occur on alternate days. The second important malarial infection is caused by *Plasmodium falciparum*. This disease has no tendency to relapse if treated vigorously with suppressive drugs but has a high mortality rate in susceptible individuals if untreated. It is called *malignant tertian malaria* and may present variable clinical manifestations.

At this point it is probably wise to define the four different properties that may be possessed by antimalarial drugs. First, they may have *suppressive* effect in which case we know, as the result of very recent research, that they act against the blood stages of the disease, which produce clinical symptoms, but do not eradicate the tissue stages of the parasites, which cause relapse. Secondly, drugs are *prophylactic* if their action is against the sporozoites which the mosquito injects or against the primary tissue stages which develop during the asymptomatic period prior to the onset of the first clinical attack. Drugs may effect only the gametocytes, the sexual parasites in the blood, which cause no symptoms in the human host but are responsible for the transmission of the disease to the mosquito when she sucks her blood meal. Finally, *curative* drugs eradicate *all* stages of the parasites and, thereby, lead to radical cure.

Quinine, the standard antimalarial drug prior to World War I, is purely suppressive in vivax infections. It affects only the blood stages and does not influence the relapse rate. It may suppress (and, thereby, cure) falciparum malaria, though some strains of parasites are highly resistant to the drug.

Plasmochin, the drug synthesized by the Germans, has several unusual qualities which were first demonstrated by British investigators in India before World War II. It is prophylactic in both vivax and falciparum infections, but unfortunately, only in extremely toxic doses. Its curative properties in vivax malaria are manifest by great reduction in the relapse rate of the disease after treatment with this drug in combination with quinine. In small doses, it abolishes the parasites which transmit the disease to the mosquito, but it has relatively little effect on the blood forms of malaria that cause clinical symptoms. Its great drawback is its toxicity which is greater in the darker skinned races and is so great in all individuals as to preclude prolonged administration in endemic areas.

The obvious toxicity of plasmochin led the Germans to continue investigations and in 1933, atabrine was developed. The enthusiasm of early reports of the effectiveness of atabrine in the field was soon dimmed by reports of severe toxicity. By the beginning of World War II, the situation was hopelessly confused as to the value of the three available antimalarial drugs. In the medical literature, one could find innumerable dosage schedules and conflicting reports as to their effectiveness and toxicity. There was not even uniformity of opinion regarding the manner in which quinine, the oldest drug, could best be administered and completely contradictory opinions existed as to the usefulness of atabrine.

Shortly after Pearl Harbor, therefore, the United States was faced with the necessity of fighting a major war in the most malaria-infested areas in the world with 90 per cent of the supply of quinine in the hands of the Japanese. Under these circumstances, the organization of an intensive program for the evaluation of available synthetic compounds and the development of new ones became a vital necessity. A group in the National Institute of Health initiated the program which grew on a national scale and finally led to international planning and cooperation under the direction of the Board for the Coordination of Malarial Studies of the National Research

Council. Through this Board, the combined efforts of military and civilian investigators were effectively integrated. Among these groups the university scientists and those in the laboratories of the pharmaceutical industry played a most important role. The program was first financed by the Office of Scientific Research and Development and since the war by grants from the United States Public Health Service. The scope of the investigations is best demonstrated by the fact that over fifteen thousand drugs have been tested for therapeutic effect in several species of avian malaria and for toxicity in animals since 1941. Over one hundred and fifty compounds have shown enough promise to warrant testing in man.

Research during the war divides itself naturally into three phases. For over a year after Pearl Harbor, primary emphasis was devoted to the search for an effective substitute for qunine. It was established, through clinical investigations in the United States and the field studies of the Australian group, that atabrine when properly administered in daily doses was far superior to quinine as a suppressive drug in vivax malaria. Atabrine effectively suppressed even the highly relapsing Southwest Pacific strain of vivax malaria and, most fortunately, not only suppressed but cured the malignant tertian disease. This superiority of atabrine and the development of proper methods of administration was a most significant factor in the winning of the second World War. It led to the practical abolition of clinical attacks of malaria in the Allied armies under fighting conditions, though four hundred thousand men were infected with vivax malaria which recurred as soon as the drug was stopped; it abolished malignant tertian malaria as a clinical problem both during and after the war; and finally, it reduced the death rate from malaria to less than one per two thousand men having the disease.

The loss of quinine therefore turned out to be a boon to us, for the Japanese continued to rely solely on the older drug which proved to be a poor suppressive drug for the Southwest Pacific strains of malaria. It is hard to understand why the Japanese failed to switch to atabrine. It is now obvious that malaria eventually fought on our side and made possible the island hopping in the Pacific which was of great strategic value. For this we can give thanks to the Germans who had the foresight to develop atabrine. In retrospect, it is now also understandable why military censorship forbade even mentioning

the word malaria except as our government's own propaganda misled the American and Japanese public jointly into believing that Japan had the advantage with her supply of quinine. The American public could not be informed of the truth without warning the Japanese of a need for a change in the antimalarial discipline.

The next stage in the investigations during the war were dictated by military considerations and consisted of a search for suppressive drugs superior to atabrine. The discoloration of the skin following its chronic administration, the development of disorders of the skin commonly called "jungle rot", and the necessity for daily administration of drugs were undesirable properties of atabrine. Highly effective nontoxic suppressive drugs were developed both in Britain and in this country. Through the combined efforts of British and Australian investigators, who studied the antimalarial properties of a series of biguanides, a most effective drug, paludrine, which in this country is also called chlorguanide and guanatol, was developed. In the United States intensive investigations of the 4-aminoquinolines which had previously been studied by the Germans led to the development of several active compounds, of which chloroquine, now sold commercially under the name of Aralen, is probably the most effective. Indeed, it may prove to be the most useful antimalarial drug today.

Chloroquine has the following advantages over atabrine. It is highly effective in eliminating blood parasites and leads to more rapid symptomatic relief during clinical attacks. It is followed by longer latent intervals after treatment of acute attacks of vivax malaria in non-immune individuals. It leads to no discoloration of the skin and is followed by fewer and milder toxic symptoms. It effectively suppresses vivax malaria in small weekly doses and will abolish a clinical attack in treatment of only one day's duration. Like atabrine, it will cure the malignant tertian disease but does not affect the relapse rate in the benign tertian infection. Although chloroquine is more expensive and a little more toxic than the British drug, paludrine, which has similar characteristics, these disadvantages are more than compensated for by the fact that several strains of malarial parasites, particularly several found in Africa, can become highly resistant to paludrine.

Oxychloroquine, camoquin and santochin, of the 4-aminoquinoline series, have antimalarial properties similar to those of chloroquine.

Santochin, though less active and somewhat more toxic than the other drugs, is of special interest because its capture by the Free French in Africa greatly stimulated the investigation of the 4-aminoquinolines in this country, which had been allowed to lag after promising but incomplete earlier studies.

Although chloroquine has marked superiority over atabrine, it was only tested in limited military operations during the second World War because reconversion to this drug would have delayed military operations during reindoctrination of the troops. At the present time, however, there should be no reason for the continued use of atabrine in view of the superiority of both chloroquine and paludrine.

The final phase in the search for better antimalarial drugs began in the latter part of 1944 and was dictated by the need for a drug that would stop relapses, that is, a drug that would produce radical cure of vivax malaria. As increasing numbers of soldiers became infected, it was feared that upon their return home serious epidemics of malaria would develop. In the earlier phases of investigations, it had been hoped that truly curative drugs could be found by increasing the potency of suppressive agents. When, however, several antimalarial drugs having far greater suppressive activity than atabrine and quinine were developed and these compounds failed to reduce the relapse rate in vivax malaria, even in maximum tolerated doses, attention was again directed to plasmochin, the only known drug having curative properties in this disease, and to its chemical relatives known as 8-aminoquinolines.

Investigations have continued until the present time, but since the end of the war, the scope of the national program has been reduced. As before, close cooperation has been maintained between investigators in universities, the pharmaceutical industry, the United States Public Health Service and the Army. The abolition of censorship and the granting of complete freedom to the investigators have proved to be an advantage which in part has made up for the smaller size of the program. In the beginning of these investigations, several new problems faced the investigators. As long as suppression had occupied the center of the stage, drugs could be tested in paretic patients who needed fever therapy to combat their disease. Such therapeutic malaria is commonly given by transfer of blood

from one patient to another, because malaria transmitted by transfusion, unlike that following the bite of the mosquito, is easy to control as it does not relapse after quinine. Obviously this makes impossible testing of truly curative drugs in blood induced infections. The need for cooperative, healthy, non-immune volunteers who would expose themselves to the rigors of repeated attacks of vivax malaria after mosquito-innoculation of the frequently relapsing Southwest Pacific malaria and to the not inconsiderable dangers of the toxic manifestations of the 8-aminoquines was a serious problem in continuing investigations.

These volunteers were chiefly found amongst the inmates of several Federal, State and Military prisons. The patriotic zeal exhibited by these inmates in participating in the war effort as experimental subjects without previous promise of reward is highly commendable. The most extensive clinical investigations in the search for curative drugs in vivax malaria were conducted at the Illinois State Penitentiary (Stateville) where over eight hundred volunteers have experienced an average of four clinical attacks each. Approximately fifty potential antimalarial compounds, most of them belonging to the 8-aminoquinoline series, have been investigated at this institution under the direction of the University of Chicago investigators with the assistance of Army Medical Officers.

Two compounds, pentaquine and isopentaquine, have reached the stage of development where it can be definitely stated that they are superior to pamaquin or plasmochin. Of these, pentaquine which received preliminary study before the end of the war, is now available commercially. It has at least as great curative effect as plasmochin and is somewhat less toxic. It will cure very heavy infections in non-immune persons in three-quarters the maximum tolerated dose if administered with quinine for two weeks. Plasmochin will cure severe infections only when administered in the largest amount that can be tolerated by man. Pentaquine will cure vivax infections in veterans, who presumably have considerable immunity, in about one-quarter of the maximum tolerated dose. This may safely be administered on an ambulatory basis under medical supervision. Isopentaquine, which is very closely related to both of the earlier drugs, is somewhat more effective on an equal weight basis than either of the former drugs and is less toxic. However, all of

these drugs still possess enough toxicity when administered to dark skinned races to limit their usefulness in the control of malaria in endemic or hyperendemic areas. They may have limited value in the field because, used intermittently in very small doses, they eliminate the sexual forms of the disease in the blood, thereby, preventing transmission of malaria to mosquitoes; but, curative drugs which we possess at present have as their chief virtue the ability to eradicate relapsing malaria completely in the traveler returning from the tropics to a malaria-free area.

So matters stand at present except for the uncertainty of several drugs which have only undergone early experimental investigation. Although some of these look promising and may eventually prove to be more universally useful than the present curative drugs, it is too early to predict their value. This includes primaquine which unfortunately has recently been heralded in the press as a "wonder drug" on the basis of far from accurate reporting.

We may summarize as follows: Although the ideal drug that would possess prophylactic, suppressive and curative properties against all forms of human malaria in nontoxic dosage was not found during the large scale investigations begun with the onset of World War II, important advances were made. We now possess several suppressive drugs of such low toxicity and great antimalarial effect that the clinical manifestations of malaria can be suppressed by weekly drug administration. These drugs also lead to radical cure of falciparum infections. Curative drugs for the relapsing disease are too toxic for administration without medical supervision in darker skinned races but can safely be administered to white persons on an ambulatory basis on their return to areas that are free of malaria.

In the problem of world malaria, drugs will probably always play a secondary, but important, role to insecticides such as DDT and to sanitary engineering projects. With the judicious use of drugs and all the other known antimalarial measures, however, it can be stated that the control of malaria in any area is no longer a medical problem but an administrative, economic, sociological and political one. Elimination of malaria is now possible wherever these factors are favorable. The new discoveries and developments can open up large areas in the tropics which previously have been closed to the white man. Improved malaria control may raise the standard of

living in many "backward countries." Malaria can now be eradicated from plantations, many native communities, at least parts of large nations and from islands if not from continents. Malaria need never again become a serious military problem. It will in all probability continue to be a devastating disease in large areas of the world for years to come, but we may now hope with good reason that it will become an extinct disease in the United States within a very few years.

A WOUND HEALING PREPARATION FROM THE LEAVES OF THE LARGE PLANTAIN (PLANTAGO MAJOR L.)

By "Dotsent" R. K. Aliev *

(Translated by Edgard Yan Allen M. S. from the Russian Periodical "Pharmatsia," Vol. 2, 1945.)

THE large Plantain (Russian: Podorojshnik Bolshoi) Plantago major L. belongs to the Plantaginaceae (Plantain) family and is distributed around roads, in meadows, fields, and in almost all the barren and weed covered sections of the U. S. S. R.

Being interested in the use of Plantain leaves in folk medicine as wound healing substances we studied their chemical composition and compounded a preparation from them for treating suppurative skin diseases. The leaves for this investigation were obtained from the Shamhorsk region of the Azerbaijan Soviet Socialist Republic.

As a result of performed phytochemical analyses it was determined that the leaves of the large Plantain contain glucosides, saponins, bitter principles (bitterness index: 1:200), tannin-like substances (1.72%), sugar substances (before hydrolysis 5.2%, after hydrolysis 6.4%), volatile oils (after hydrolysis 0.1%), resins, chlorophyll, alkali and alkaline-earth metals, vitamins A, C and K.

Alkaloids, anthraglucosides, starch and vitamin D were not observed in the composition of the large Plantain leaves.

Content of ash in the leaves was from 12% to 14.3%; moisture 8.02%; acid 2.3%. From the list of substances contained in large Plantain leaves special attention should be focussed upon the glucosides, saponins, tannin-like substances, and vitamins A, C and K.

For treating suppurative skin diseases an ointment of the following composition was prepared from the leaves:

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Pulveris foliorum Plantaginis majoris (Powdered large Plantain leaves)	10 parts
Olei persicorum q. s. Vaselini albi depurati (Oil of Persic q. s. with Purified White Vaseline)	90 parts

NOTE: "Parts" represents parts "by weight" in this formula.

In order to prepare this ointment it is necessary to take 10 parts of large Plantain leaf powder obtained by triturating the dry leaves in a clean porcelain mortar and then screen through a No. 1 sieve.

Specifications for a Number 1 sieve employed in Russian Soviet pharmaceutical practice:

Threads per one square centimeter	50
Openings per one square centimeter of sieve material	2500
Designation customary in foreign literature	M/50
Thickness of threads in millimeters	0.08 mm.
Usual width of mesh in millimeters	0.12 mm.
Sieve material	Silk Cloth
Designation of Powder	Pulvis subtilissimus Finest Powder

The powder must have a dark green color at this stage. The powder is well triturated with a small quantity of some indifferent fixed oil (Oil of Apricot, Oil of Persic, Almond Oil or others). Then 90 parts of purified white vaseline are added and the ingredients are thoroughly mixed until a uniform mass is obtained. The prepared ointment must have a dark green color, a uniform thick consistency and almost no odor. It must be stored in a dry place in well-closed porcelain and glass containers. The preparation of this ointment for storage in stock for an indefinite length of time is not expedient. It is better to prepare it ex tempore.

Clinical investigations of large Plantain leaf were carried out at the Azerbaijan Skin-Venereal Institute under the direction of Professor B. Eivazov. These investigations showed that:

1. Due to the action of the ointment there occurs a rapid separation of the pus from elements of impetigo and ecthyma, and a counter action against them is started.

2. The ointment exhibits an anti-inflammatory action and affects epithelialization and destruction of the elements of impetigo and ecthyma of the skin.

3. Analyses of the serum and blood before and after application of the ointment were made. No injurious side reactions on internal organs were observed in these tests.

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TRANSLATOR'S NOTICE: The sieve specifications are not included in the original article. I have included them as further information and help to any pharmacist in the United States of America who may desire to compound this medicament.

E. Y. A.

SELECTED ABSTRACTS

Effect of Tetrethylammonium Bromide on Gastric Secretion and Motility. I. R. MacDonald and A. N. Smith. *Brit. Med. J. No. 4628*:620 (1949). The site of action of tetra-alkyl-ammonium compounds is at the ganglionic synapses of the autonomic nervous system. At this site tetraethylammonium bromide (T. E. A. B.) produces a blocking effect probably because it can replace acetylcholine in the neurohumoral chain at the autonomic synapse.

Investigating the effect of T. E. A. B. on gastric secretion and motility the authors found that this drug does produce a slight fall in gastric acidity and in the volume of night secretion. The presence of a vagal blockade by the drug was shown by the fact that the induction of insulin hypoglycemia failed to stimulate a rise in gastric acidity. It was also found that the normal stimulation of gastric secretion following the administration of histamine was substantially reduced by T. E. A. B. Since histamine acts directly on the oxyntic cells this effect cannot be due to autonomic blockade. It was felt that this reduction in acidity was due to the fact that the stomach was relatively amotile with accompanying retention, and therefore, there was greater buffering of the gastric secretion by alkaline and mucoid elements in the stomach contents. The average reduction in milliequivalents per hour was 80 per cent as compared with a reduction of 90 per cent following anatomical section of the vagus. The effect on gastric motility was similar to that obtained by vagotomy when tested on 5 ulcer patients. The volume and acidity tests were performed on 10 ulcer patients.

These effects obtained following the administration of T. E. A. B. intravenously or intramuscularly, and particularly the nocturnal volume and acidity effects, has raised hope that this compound may be of value in the treatment of peptic ulcer in man. The authors pointed out also that all 10 of the ulcer patients were free of pain during the progress of the experiments in which they received T. E. A. B. The disadvantages of the drug are that it must be given by injection and also that it produces subjective symptoms such as flushing, transient and peripheral numbness and impairment of the power to urinate or defecate, and lightheadedness.

Microbiological Assay for Vitamin B_{12} Using Lactobacillus Lactis Dorner. G. E. Shaw. *J. Pharm. Pharmacol. 1:695* (1949). In 1947 Shorb had announced that *Lactobacillus lactis* Dorner responded to a factor present in liver extracts to an extent roughly proportional to their clinical value. This has opened the possibility of the use of this organism for a microbiological assay for vitamin B_{12}. Following considerable research along these lines the author has reported an assay procedure which has proven to give regularly reproducible results over a long period of time.

The principles used in the final method are those which are influential in all other microbiological assays. The test inoculum must be minimal; the organisms in the test inoculum must be young, in a very active phase of growth, and have been maintained on a complete medium; and the medium must have been free from other growth factors.

The basal medium is composed of sulfuric acid-hydrolysed casein with added tryptophane, the vitamin B complex, and Tween 80. The final medium is adjusted to a pH of 5.5, and the glucose, potato extract and the preparation to be tested are added aseptically to the previously autoclaved basal medium. A suspension of the test organism is carefully prepared and added to the test medium. It is interesting to note that the organism must not remain suspended in the saline for more than 1½ hours or the characteristics of the organism will be changed. Incubation usually requires about 18 hours but as much as 48 hours may be necessary. The length of time of incubation does not affect the assay results. It is necessary to use constant bore test tubes in order to have a constant surface area to volume ratio. After incubation the growth is determined photometrically.

Growth response curves are then prepared using about 5 concentration levels of the vitamin B_{12} preparation and plotting the concentration as the abscissa and the photometer reading as the ordinate.

Four substances with growth activity for *L. lactis* Dorner may be present in liver extracts. These may be separated by means of paper strip chromatograms. Two of the factors have anti-pernicious anemia activity and two of them do not. Thus one form of interference can be eliminated.

The Influence of the Dosage Regimen on the Therapeutic Activity of Penicillin G. L. H. Schmidt, A. Welley, and R. D. Larson. *J. Pharmacol. 96*:258 (1949). The authors performed a quantitative study to determine the effectiveness of various dosage regimen of penicillin G against a fulminating pneumococcal infection in the white rat.

The results of the study showed that when the treatment interval is of a short duration, of 8 hours or less, 2 doses of sodium penicillin G administered 2 or 4 hours apart were considerably more effective than a single dose or 2 doses given at an interval of 8 hours. When the treatment interval was about 96 hours, divided doses of the sodium salt given at intervals of 2, 4, or 8 hours were far more effective than divided doses given at intervals of 12 or 24 hours. The study also revealed that, although procaine penicillin G was significantly more effective than the sodium salt when administered at intervals of 24 hours, the procaine salt at the 24 hour interval was not as effective as the sodium salt administered at intervals of 2, 4, or 8 hours.

A study of the blood level of penicillin showed that equally effective doses of both salts maintained inhibitory concentrations of the antibiotic for only a small fraction of the dosage interval. These findings definitely show a relationship between the dosage interval and the effectiveness of therapy with both salts of penicillin G, but they do not substantiate the general assumption that effective therapy is dependent upon the maintenance of continued inhibitory concentrations of penicillin in the blood. Instead, these results showed that the administration of water soluble salts of penicillin administered at fairly wide intervals may achieve optimum therapeutic effectiveness.

The Role of Carbohydrates in Dental Caries. G. H. Green. *U. S. Nav. Med. Bull. 49*:920 (1949). Since less than 50 per cent of the persons in the United States who are over 35 years of age have a usable number of natural teeth, it is evident that dental caries pose a definite public health problem.

There are two theories of the formation of dental caries. The first is the acidogenic theory, which states that caries result from decalcification of the enamel and dentin caused by degradation of carbohydrates to acid which in turn is followed or accompanied by

proteolysis of the organic matrix. The second theory, known as the proteolytic theory, states that caries result from proteolysis of the organic substance of the enamel and that acid action resulting from carbohydrate degradation is a component of the process. Thus, acid formation from carbohydrates is an important part of either of these theories. These acids are formed in protected areas of the mouth by a series of enzymatic reactions, the enzymes for which are formed by the acidogenic micro-organisms of the mouth and by co-enzymes found in certain natural components of the diet. Acid is thus formed in all mouths when a suitable substrate is present. When acids are formed faster than the acid-neutralizing action of the mouth can overcome them the teeth become decalcified in the protected areas. The substrate from which the acid is formed must be a fermentable carbohydrate. It has also been shown that the carbohydrates form a growth factor for the bacteria which bring about the acid production. In addition carbohydrates produce a systemic effect by bringing about a change in the saliva which in turn provides a more favorable medium for the growth of the acid-forming bacteria such as *Lactobacillus acidophilus.*

Starches are but slowly converted to sugars in the mouth and never very completely during the short times in which they are in the mouth. Therefore, the monosaccharides and the disaccharides are of greatest concern. It has been shown that fructose, glucose and sucrose can cause a decrease of about 0.8 pH in the mouth within 5 minutes. These sugars are found, not in any high concentration in the natural state, but in the refined state in jams, candies, ice cream, bakery products and the like. Thus, in the control of dental caries the adoption of a low-sugar diet is one of the best and most direct methods which may be recommended.

Dental caries activity can be reduced 70 to 90 per cent by the adoption of low sugar diets. The topical application of sodium fluoride has also been shown to be a means of reducing dental caries as much as 40 per cent. The use of a dentifrice containing dibasic ammonium phosphate and urea along with proper oral hygiene also has proven to be beneficial in reducing dental caries. These newer methods of prevention and the increased understanding of the etiology of caries suggest that this widespread public health hazard may soon be brought under control.

A New Mechanism of Vitamin Deprivation With Special Reference to the Sprue Syndrome. A. C. Frazer. *Brit. Med. J.* No. 4630:731 (1949). The striking selectivity of vitamin deficiency in patients with sprue is confined to the B vitamins, nicotinic acid, riboflavin, pyridoxine, and folic acid which are essential growth factors for bacteria. Investigation of the other known mechanisms for vitamin deficiency; dietary inadequacy, faulty utilization, defective absorption, or faulty digestion of vitamin precursors has shown that they do not explain the vitamin deficiencies which accompany sprue.

It has been shown that there are large numbers of bacteria within the absorbing areas of the small intestine. Also, it is known that these bacteria will absorb essential vitamins and other factors. The author therefore offers the competition hypothesis as an explanation of the vitamin B deficiencies which accompany sprue. He suggests that from time to time the bacteria invade the upper small intestine in very large numbers and, there, compete with the host for the vitamin supply. In such cases they are at least temporarily the victors over the host, and the host develops symptoms of vitamin deprivation. At the same time they produce the bulky fermenting stools. The occasion of the bacterial invasion may be related to fixation of pH as a result of achlorhydria and possibly the presence of suitable food materials due to delayed absorption. This also may be coordinated with the intermittent exacerbation of clinical symptoms, especially diarrhoea accompanied by deficiency signs, particularly those affecting the tongue and eyes, so characteristic of sprue.

Oral therapy for vitamin B deficiencies in sprue requires extremely high dosage. This may be accounted for in that sufficient must be given to supply both the bacteria and the host. Parenteral administration of small doses of the proper vitamin fractions produce dramatic curative results, however.

While the author was primarily concerned with the vitamin deficiencies in the sprue syndrome, he also pointed out that the intestinal competition of bacteria with the host may be an important factor in the vitamin deficiencies which accompany other disease conditions. He particularly mentioned the vitamin B deficiencies which accompany pernicious anemia. Although there seems to be no absorptive defects in pernicious anemia such as are found in sprue, it is possible that the absence of absorptive defects and consequential

environmental differences may result in qualitative and quantitative modifications of the intestinal flora with resultant differences in metabolic demands. The metabolic demands of a varying but essentially non-pathogenic bacterial flora in the intestine may be the key to the problem of the multiple but selective vitamin deficiencies so commonly observed in these and similar disease conditions.

The Antibacterial Activity of Sodium Lauryl Sulfate. M. Witt. *Austral. J. Pharm. 30*:674 (1949). A study of the effectiveness of sodium lauryl sulfate in preventing bacterial growth in concentrations normally used in pharmaceutical preparations indicates that such concentrations of the surface active agent are bactericidal against the Gram-positive organisms tested. The Gram-positive organisms used in the tests were *Clostridium welchii, Streptococcus pyogenes A,* and *Staphylococcus aureus.* Tests on two Gram-negative organisms, *Bacterium coli* and *Proteus vulgaris,* indicated that concentrations of less than 1:10 did not prevent bacterial growth. The concentrations which prevented all growth of the Gram-positive organisms were 1:1600 and above.

The author used tubes containing meat infusion broth to which the various increments in concentration of sodium lauryl sulfate were added. These tubes were then inoculated with the test organism and incubated for 48 hours at 37 C. Sterility controls and controls to test the viability of each organism were also set up at the same time. Because the tubes were all turbid each tube was plated on sheep blood agar and the plates also incubated for 48 hours at 37 C. The end point then taken was the highest dilution of sodium lauryl sulfate which completely prevented visible growth on the blood agar plate.

Method for Measuring Diffusion of Antiseptics From Ointment Bases. G. H. Clark and G. E. Davies. *J. Pharm. Pharmacol. 1*:521 (1949). Methods which have been developed for the measurement of the diffusion of medicinal substances, particularly antiseptics, from various types of ointment bases have not been too satis-

factory. The most common method for *in vitro* testing, the agar cup plate method, has a number of disadvantages. There is usually a minimum period of 24 hours contact between the ointment and the agar, and thus it is not possible to determine the diffusion over a shorter period. It is difficult to fill the cups to the same degree each time, and thus it is not easy to duplicate results. Another drawback is that not all antiseptics penetrate the agar gel in the same way.

A new method of testing different rates of diffusion over a shorter time interval is based upon the diffusion of an active ingredient from an ointment base through cellophane onto inoculated agar. The minimum time of contact sufficient to cause inhibition of bacterial growth is recorded.

Briefly the method is as follows: 10 cc. of agar is poured into a petri dish and dried. A layer of agar (5 cc.) containing 1 cc. of a 1:10 broth dilution of a culture of *Staphylococcus aureus* is poured onto the previous layer of agar. With sterile forceps 1 inch squares of sterile cellophane are placed on the agar. The plates are incubated for 45 minutes, which causes the cellophane to spread out evenly. A disc of filter paper is trapped in the lid of the dish to absorb moisture. A hypodermic syringe without the needle is used to apply the material to be tested on the cellophane, leaving a 1/8" border. The dish is placed in the incubator and the cellophane squares removed at suitable intervals. After incubation over night the plates are examined for growth inhibition, indicated by clear areas in the agar under the previous locations of the cellophane squares.

No difficulty was experienced in duplicating results. In tests of several type ointment bases containing phenylmercuric nitrate the minimum time of contact for inhibition of bacterial growth was 2 minutes from a jelly base.

The Treatment of Amebiasis With Aureomycin. L. V. McVay, R. L. Laird, and D. H. Sprunt. *Science 109:*590 (1949). The treatment of human infections by the parasite *Endamoeba histolytica* has been unsatisfactory, particularly because of the danger of toxic reactions from current treatment procedures.

A preliminary report was presented by the authors of the results of the treatment of this infection with aureomycin. Three cases were reported but the results were very encouraging. The first patient had negative stools after the oral administration of 7 Gm. of aureomycin in divided doses over a 3-day period. Treatment was continued until a total of 19 Gm. was given. The second patient had negative stools following the administration of 6.75 Gm. over a 3-day period, but therapy was continued until 21.75 Gm. had been given. The third patient received 15 Gm. of the antibiotic before the stools became negative. A total of 22.7 Gm. were given altogether. In each case a number of negative stools have been obtained after the end of therapy. No stool was reported negative until it had been studied by fresh saline and iodine preparation, by iron hematoxylin stain, and by culture. The only reaction encountered was nausea for about 48 hours after the initiation of treatment in the third patient.

In vitro tests showed that all of the ameba in culture tubes to which had been added 0.8 mg. or more of aureomycin per cc. were killed by the end of 6 hours contact. Most of the ameba were killed in the presence of 0.2 or 0.4 mg. per cc. after 18 hours exposure. Following 48 hours exposure to the antibiotic no ameba were found in any of the tubes but the control cultures were heavily infected.

Evaluation of the Mumps Skin-Test. A. L. Florman, A. E. Fischer, and R. E. Moloshok. *Clinical Research Meeting at the New York Academy of Medicine June 1949.* Skin tests were performed on 135 individuals among whom 26 were first cases of mumps and the rest were contacts. Among the contacts there were 80 adults and 29 children. The antigen used was formalin killed egg grown virus partially purified by centrifugation. Intradermal inoculation produced a tuberculin-like reaction in those patients who have had clinical or inapparent mumps previously.

The reactions were often difficult to read, particularly among children. All of the patients with a first case of mumps gave negative reactions during the illness, but several months later 5 of 6

retested were clearly positive and 1 was quentionably so. Among the contacts there were 60 positive and 49 negative skin tests.

Within 3 weeks 12 of the contacts became ill with clinical mumps. Only one of these had previously given a positive test but 10 of the remaining 11 who had given negative reactions previously were children. The authors concluded that, although the test is useful in determining the susceptibility of individuals to mumps, a positive skin reaction is not a sure indication of resistance.

The Therapeutic Use of Phthalylsulfacetimide in Cholera. H. Seneca and E. Henderson. *The Am. J. Trop. Med. 29*:425 (1949). The principal therapeutic problems in the treatment of cholera are the restoration of fluid, salt loss and the eradication of the infecting organisms. No control cases were studied along with those treated in this study but there was an overall mortality rate of 49.4 per cent during the epidemic of which the treated group of patients was a part.

Interest in the use of phthalylsulfacetimide arose from the observation that this drug was very effective against *Vibrio comma in vitro*. Another property of this sulfonamide aroused interest in its application to the treatment of this disease. Phthalylsulfacetimide has the unique property of being absorbed into the layers of the intestinal wall without being absorbed into the blood stream. Thus there could be obtained a concentration of the drug at the very locus of the infection without the necessity of obtaining this concentration by means of a high systemic level with its possible accompanying toxicity. Other treatments also provide only a high concentration of the therapeutic agent in the bowel contents and, thus, give merely a washing effect upon the locus of infection.

The drug was used for the treatment of 40 patients of whom 39 survived. In general the drug was given initially in a dose of 5 Gm. and subsequently in a dose of 1 Gm. every 2 hours day and night for 5 days. Saline infusions were also given as well as fluids orally. The vibrios disappeared from the stools promptly, and there was a gradual clinical improvement. Recovery ensued and the patients were discharged to convalescent care after an average of 14 hospital days.

The possible use of this drug as a prophylactic was considered because of the rapid disappearance of the cholera vibrios from the stools following treatment. A small section of the populace was treated prophylactically during the epidemic, but the experiment failed because of inability to observe the persons treated. However, the authors felt that this drug would be effective prophylactically if properly trained personnel were available to oversee the treatment.

The Use of Decamethonium Iodide as a Muscle Relaxant in Anesthesia. A. J. H. Hewer, B. C. B. Lucas, F. Prescott and E. S. Rowbotham. *Lancet 256*:817 (1949). A satisfactory curarizing effect was produced in 85 surgical patients by the intravenous administration of 3 to 5 mg. of decamethonium iodide (decamethylenebis (trimethylammonium iodide)) followed by additional doses of 1 to 3 mg. as needed. In some cases the dosage was based upon body weight, that is, 1 mg. per Kg. as an initial dose followed by ½ to ⅓ of this amount. The total dosage employed was 3 to 15 mg. The anesthesia administered was usually the intermittent combination of thiopentone, N_2O and O_2.

The effect from this drug began to appear within 2 to 3 minutes with the attainment of a peak effect within 4 to 8 minutes. The effect, comparable to that produced by *d-tubocurarine*, lasted for a period of 15 to 25 minutes. As little as 3 mg. produced paralysis of the muscles of respiration. The authors pointed out that tidal air returned to normal within 3 minutes of the onset of recovery. They also stated that there were no cumulative effects even though the relaxation was maintained for as long as 3 hours. There were no significant side effects observed from the use of this new compound. In 4 cases there was a postoperative period of restlessness which lasted for about 24 hours.

A volunteer was given a dose of 2 mg. while conscious. He experienced cramping pain and tenderness in the limbs which lasted for several hours. Exercise seemed to increase the pain. Pentamethonium iodide was not effective as an antidote when given experimentally.

Effect of Surface Active Agents on 2,4-D Sprays. D. W. Staniforth and W. E. Loomis. *Science 109:*628 (1949). The authors investigated the effects of adding various surface active agents to sprays of 2,4-dichlorophenoxyacetic acid used as an herbicide. The toxicity of the sodium and amine salts of 2,4-D to corn, flax, and soybeans was increased five or more times by the addition of about 1 per cent of commercial non-soap wetting agents. The authors felt that the action was probably not chemical in nature since various types of wetting agents gave the effect. They suggested that decreased surface tension and increased pentration of the sprays seemed to be the most likely answer. However, they felt that the reason for this increase in toxicity is not a simple relationship, for a non-ionic wetting agent was ineffective in increasing the toxicity on corn but effective on soybeans. An ionic agent of the lauryl sulfate type gave an increased response up to concentrations of 2 per cent of the agent in 2 2,4-D spray, but the surface tension of the spray did not vary significantly after the first 0.05 per cent of the wetting agent had been added.

The effect of the combination of the 2,4-D and various wetting agents has been to increase the speed and severity of injury to the plants but not to hasten death. No corn nor flax plants were killed during these experiments for each are naturally moderately resistant to the action of 2,4-D. The authors point out, therefore, that the primary effect of the wetting agents seems to be to reduce the selective action of the herbicide. Therefore, the authors offer the warning that great care must be exercised in the use of wetting agents in combination with 2,4-D for by this combination the usefulness of 2,4-D in killing susceptible weeds with little injury to resistant crops is reduced.

The Blood Levels Obtained With Procaine Penicillin With Aluminum Monostearate. J. L. Emery, L. M. Rose, S. M. Stewart, and E. J. Wayne. *Brit. Med. J. No. 4616:*1110 (1949). The authors reported the results of a study to determine the blood levels of penicillin obtained following the intramuscular injection of graded doses of procaine penicillin in arachis oil with 2 per cent aluminum monostearate. In this preparation 95 per cent of the particles were

under 5 μ in diameter since it has been found that this small size prolongs the rate of absorption.

The dosage employed in the 66 children studied was graded to the age level. Children under 1 year received either 75,000 or 150,000 units of penicillin, children from 1 to 4 received 150,000 units, and children over 4 received 300,000 units of penicillin per dose.

The authors found that there was a rapid initial absorption of penicillin giving a level above 0.2 units per cc. by the end of the first hour. This level was maintained for about 3 hours. In all but one patient a level of at least 0.06 units per cc. was maintained for 48 hours, and in 20 of 22 patients examined at the end of 72 hours this minimum level had been maintained. From this observation it was assumed that injections on alternate days should maintain a blood level of at least 0.06 units per cc. This was found to hold true in 8 children given an injection on alternate days. The question was also considered as to whether or not the daily injection of the penicillin preparation would produce a cumulative effect. This also proved to be true for the majority of children given daily injections maintained blood levels of penicillin above 0.1 units per cc. This concentration is bacteriostatic for almost all pathogens.

The disadvantage of this preparation is its oily nature and also the possibility of sensitization. The authors reported that they had not observed any adverse reaction to the preparation. The advantages which may be offered for the preparation are an almost painless injection site, minimal local and no general reaction, and an almost stable concentration of penicillin in the blood for at least 48 hours.

The Experimental Determination of the Changes in the Thyroid Gland Following High Dosages of Radioactive Iodine. A. Gorbman. *Trans. The N. Y. Academy of Sci. 11*:201 (1949). The use of radioactive iodine as an agent for the control of thyroidal overactivity or cancer raises the question as to the amount of thyroid injury that may be expected from a given amount of I^{131} and also the amount of injury to neighboring tissue by radiation emanating from the thyroid gland. In an effort to throw some light

upon this subject the author performed experiments on mice weighing between 20 and 25 Gm. The thyroid glands of these animals had an average weight of 5 mg. The doses employed were 100, 200, 400, or 1000 microcuries of I^{131} injected subcutaneously. It had been found previously that the uptake of the injected radioiodine was between 5 and 10 per cent with the maximum being reached between 12 and 24 hours. The biological half life in the thyroid was found to be about 2 days. Calculated roughly the radiation dose was about 26,000 equivalent roentgens for the 100 μ c. dose and 75,000 equivalent roentgens for the 200 μ c. dose. The radiation dose was not calculated for the other doses.

The mice were sacrificed at intervals of 2, 3, 7, 24, 120, and 300 days after the dose of radiodine, but none of the animals given 1000 μ c. survived beyond a week, and those given 400 μ c. usually died within one month. Of the animals which were killed after 2 or 3 days the animals which had received 100 μ c. revealed only minute pycnosis of the follicular cells. The animals which had received 200 μ c. exhibited more extensive epithelial pyconsis, periglandular edema, and swelling of the endothelial cells of intrathyroidal blood vessels. The animals receiving the 1000 μ c. doses exhibited complete destruction of thyroid and parathyroid tissue. Examination of the thyroid glands of mice sacrificed at the end of 24 days showed surviving thyroid tissue only in the mice which received 100 and 200 μ c. doses. More tissue survived among the mice which received the smaller dosage but even here only a small amount of tissue around the edge of the gland survived. After 120 days surviving thyroid tissue was found only in the mice which received 100 μ c. The cells which were found were atypical and few in number in a shrunken fibrous band of tissue. These cells were shown by radioautographs to metabolize a very small amount of iodine but even after 400 days there was no evidence of regeneration in these cells.

Supersaturation of Calcium Gluconate in Water. S. B. Sengupta. *Pharm. J. 163*:163 (1949). A study of the supersaturation of calcium gluconate in water was performed by the author. He found that the average amount of calcium gluconate found in 100

cc. of supersaturated solution was 3.57 Gm. at 30° C., 8.8 Gm. at 65° C., 14.4 Gm. at 80° C. and 29.0 Gm. at 100° C. This was attained after the flask containing the salt and water was shaken in a rocking device in a constant temperature bath for 4 to 5 hours. A 25 per cent solution sealed in neutral glass ampuls precipitated in more than 8 hours when stored at 0° C. but in 150 minutes when stored at 30° C. Refluxing a solution had an effect upon the stability of a supersaturated solution, for after being refluxed for 5 hours and then stored at 30° C. the length of time required for precipitation to occur was increased from 150 to 420 minutes.

The author also studied the effect of added stabilizers on the precipitation time of 25 per cent solutions of calcium gluconate. He found that a 1 per cent concentration of boric acid produced the greatest stabilization but that such a solution was painful when injected. A 1 per cent concentration of calcium *d*-saccharate or of camphosoulfonic acid proved satisfactory and increased the time of precipitation to 24 and 12 hours, respectively. The mechanism of the stabilizing action was not known for the stabilizers did not increase the solubility of the salt to any great degree. The lowering of the pH of the solution did not explain the stabilizing effect for lactic acid had no stabilizing effect at all.

An Examination of Pyrogen From Various Sources. D. W. Wylie and J. P. Todd. *J. Pharm. Pharmacol. 1*:818 (1949). The subject of pyrogens is still much in the realm of the unknown. Whether bacteria, in general, produce the same pyrogenic substance or each bacterial species is a specific pyrogen is one of the unknown phases of this subject. The authors have, however, added another contribution to our understanding of the nature of pyrogens.

Previously it had been observed that different types of fever curves were obtained following the injection of pyrogenic substances, notably, the single and the double-peak curves, and the delayed reaction type of curve. Significant differences in the first two types of curves had not been observed. The authors suggested that this may have been because of taking the temperature of the rabbits at one hour intervals only.

As this investigation progressed evidence accumulated to the effect that differences in the curves were significant and were not caused by biological variation but by actual differences in the constitution of the pyrogens. The injection of a sterilized whole culture caused a double-peak fever curve. However, a cell-free filtrate or the supernatant liquid caused a single-peak curve if the cells are removed before autoclaving but a double-peak curve if the cells are removed after autoclaving. A suspension of the cells produced a single-peak fever of the delayed reaction type.

This would indicate that certain bacteria probably produce two pyretic substances. One substance is probably liberated in the culture medium and is thus contained in the filtrate. This produces a single-peak fever of the immediate reaction type. A second substance, producing the delayed reaction type of fever, is probably contained within the bacterial cell. A mixture of both of these substances then causes the double-peak fever.

Proteus vulgaris and *Ps. fluorescens* were shown to produce a substance which either lowers the body temperature below normal or prevents the pyrogen from causing a rise in body temperature. This substance is volatile and can be eliminated by heating the solution to between 30 and 40°C. for about 10 minutes before injection. Further tests showed that this volatile material caused general paralysis if injected in large quantities. In small quantities it caused a loss of appetite by the rabbits.

An investigation of the thermostability of the pyrogenic substances produced by various bacteria revealed that the pyrogens produced by *P. vulgaris, Ps. aeruginosa,* and *B. subtilis* were destroyed to a degree of about 95 per cent when heated for 2 hours at a temperature of 120°C. The pyrogen produced by *M. tetragenes* was much more thermostable, losing only about 20 percent of its activity after 2 hours of heating at 120°C.

BOOK REVIEWS

Organic Reactions—Volume V. Roger Adams, Editor in Chief, viii + 446 Pages, New York, 1949. John Wiley and Sons, Inc. $6.00.

Reviews of such an authoritative collection of information as this become little more than publication notices because of the extensive reviews of earlier volumes. The goal of the series, familiar to many, is to systematize the complex literature of organic reactions so that it can be readily utilized. This book continues the high excellence apparent in the first four volumes.

The reactions considered are: The Synthesis of Acetylenes; Cyanoethylation; the Diels Alder Reaction—Quinones and other Cyclenones; the Shiemann Reaction; the Friedel Crafts Reaction with Aliphatic Dibasic Acid Anhydrides; the Gatterman Koch Reaction; the Leuckhart Reaction; Selenium Dioxide Oxidation; the Hoesch Synthesis; and the Darzens Glycidic Ester Condensation.

Individuals concerned with any of the various phases of organic chemistry will welcome the new addition to this valuable reference work.

N. HALL

The Givaudan Index—Specifications of Synthetics and Isolates for Perfumery. First Edition, 378 pages; Givaudan-Delawanna, Inc., New York, N. Y. $5.00.

This new book was published on the occasion of the twenty-fifth anniversary of the establishment of Givaudan-Delawanna, Inc. in the United States. It is unique in its scope since no other publication gives in such concise style the information on perfume components. A long series of synthetic chemicals and isolates are described in monograph style with their structure; French, German and Spanish names; occurrence; odor; physical and chemical properties; storage; and uses described.

A book such as this is most useful and data of this nature is difficult to collect from the usual sources. The Givaudan-Delawanna organization is to be commended on rendering this needed service and we predict that the book will be very well received. It should prove sufficiently popular to warrant its continuation in successive editions in the future.

L. F. TICE

Advanced Organic Chemistry. By G. W. Wheland. Second Edition. 799 Pages Incl. author and subject index. John Wiley and Sons, Inc., New York; 1949. Price: $8.00.

The student of organic chemistry, in early courses, learns and observes numerous facts. This text is designed for the more advanced student to assist him in explanation of these facts on the basis of underlying theories. The reader's familiarity with elementary organic and physical chemistry is presupposed.

Author Wheland uses the structural theory to correlate principles and certain generalizations. His treatment of the subject matter emphasizes specific example and avoids excessive use of the often confusing term "R". A singularly outstanding feature of the book is the clear presentation of many currently unsolved questions as they are encountered.

The contents are developed logically and progressively. "Some Fundamental Concepts", such as bonds and bond types and the forces which act between atoms and molecules, serve as an introduction. This background information is then used to develop discussion of Addition Compounds, Modern Concepts of Acids and Bases, Structural and Stereoisomerism, the Configuration and Stereochemistry of Carbon and Other Elements, Electrostatic Effects in Organic Chemistry, Molecular Rearrangements, Tautomerism and Free Radicals.

Both the teacher and student of advanced organic chemistry have long felt the need of a generally available, unified textbook of this type. It should, therefore, enjoy wide use by those individuals for whom it was designed.

N. HALL

Antibiotics. Edited by G. W. Irving and H. T. Herrick. Chemical Publishing Co., Inc., Brooklyn, N. Y.; 1949. $6.75.

This book is a collection of lectures on the Progress in the Field of Antibiotics sponsored by the United States Department of Agriculture Graduate School in Washington during the period September, 1946 to January, 1947. The lectures are presented essentially in the form in which they were delivered, but were revised to eliminate overlapping and to make them more comprehensive.

The adequacy of coverage leaves much to be desired, since some aspects of the field of antibiotics have been discussed thoroughly, some sketchily, some repeatedly, and some not at all.

A perusal of the subjects of these lectures reveals the omission of information on the chemistry of penicillin. This was due to the fact that at the time of these lectures, detailed information was being withheld by the Committee on Medical Research, Washington, and the Medical Research Council, London.

There are fourteen lectures which include an introduction; the history, production and certification of penicillin, streptomycin, tyrothrycin and gramicidin; possible sources of other antibiotics; and the clinical use of antibiotics in human and veterinary medicine.

In spite of the obvious shortcomings of a compilation of this type, it is felt that the book does make available to those interested in the field of antibiotics a valuable milestone in the history of its development, especially since the contributors are those who were engaged during the past twenty years in the development of antibiotic agents that have preceded and followed penicillin.

Bernard Witlin

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